Resilience and cross-network connectivity: A neural model for post-trauma survival

Running title: Resilience and functional connectivity in PTSD

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Abstract

Literature on the neurobiological bases of Post-Traumatic Stress Disorder (PTSD) considers medial Prefrontal cortex (mPFC), a core region of the Default Mode Network (DMN), as a region involved in response regulation to stressors. Disrupted functioning of the DMN has been recognized at the basis of the pathophysiology of a number of mental disorders. Furthermore, in the evaluation of the protective factors to trauma consequence, an important role has been assigned to resilience. Our aim was to investigate the specific relation of resilience and PTSD symptoms severity with resting state brain connectivity in a traumatized population using magnetoencephalography (MEG), a non-invasive imaging technique with high temporal resolution and documented advantages in clinical applications.

Nineteen Trauma Exposed non-PTSD (TENP) and 19 PTSD patients participated to a resting state MEG session. MEG functional connectivity of mPFC seed to the whole brain was calculated. Correlation between mPFC functional connectivity and Clinician Administered PTSD Scale (CAPS) or Connor-Davidson Resilience Scale (CD-RISC) total score was also assessed.

In the whole group, it has been evidenced that the higher was the resilience, the lower was the cross-network connectivity between DMN and salience network (SN) nodes. Contrarily, in the TENP group, the negative correlation between resilience and DMN-SN cross-interaction disappeared, suggesting a protective role of resilience for brain functioning.

Regarding our findings as a continuum between healthy and pathological after trauma outcomes, we could suggest a link between resilience and the good dialogue between the networks needed to face a traumatic event and its long-term consequence on individuals' lives.

Keywords: Resting State Functional Connectivity (RSFC); PTSD; Resilience; Magnetoencephalography (MEG); Salience Network (SN); Default Mode Network (DMN)

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a psychiatric disorder characterized by intense fear due to the continuous reliving of the past trauma, exaggerated responses to emotionally negative stimuli, and tendency to misinterpret innocuous stimuli as potential threats (1).

The functional topography of fear processing in PTSD patients has been largely explored with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Due to its role in the processing of emotional stimuli and in the triggering of homeostatic neurovegetative responses to stress, amygdala activation has received special attention: increased amygdala response to emotional and neutral visual stimuli was observed in PTSD patients compared to control subjects (2-4). Furthermore, medial Prefrontal cortex (mPFC) plays a key role in the modulation of emotional response through amygdala inhibition (5-7). The traditional model of neural mechanisms underlying PTSD suggests that hypoactivation of the mPFC results in a loss of top-down inhibitory control and amygdalar hyper-responsivity that, in turn, generate trauma reliving and hyperarousal (8, 9). In a more recent formulation of PTSD neurocircuitry, the attention has been moved from the neural basis of fear response to the more general role of mPFC in emotion regulation, social cognition and self-referential processing (6, 9). The Anterior Cingulate cortex (ACC) and mPFC activity has been observed in several studies, and their involvement in stress response, traumatic reminders, emotion regulation has also been supposed (10-13). Furthermore, mPFC, together with Precuneus and bilateral inferior parietal cortex, represents a core region of the Default Mode Network (DMN) (14, 15). The network study, based on resting state functional connectivity, has indeed reached a growing importance for both diagnosis and prognosis. A more in-depth knowledge of this network has been suggested as a useful approach in psychiatric patients, due to its more efficient discriminatory power with respect to measurement of regional differences (16, 17). Specifically, disrupted functioning of the DMN has been recognized at the basis of the

pathophysiology of a number of mental disorders, such as schizophrenia, anxiety, depression and PTSD (13, 18-21). So far, several results indicating altered within-DMN connectivity in PTSD patients have been reported (see Peterson et al., 2014 for a review) (22). Interestingly, DMN alteration has been hypothesized to be at the basis of some PTSD symptoms, including exaggerated emotional response and misperception of benign stimuli as potential threat, because of a loss of efficiency in the internal modulation of these responses (23).

In the same framework, the neurocircuitry underlying several mental disorders seems to be better understood considering large-scale brain interactions between different networks. Menon (2011) (23) proposed that alteration in the interaction between DMN, Salience Network (SN) and Central Executive Network (CEN) may cause a maladaptive individual-environment interaction. Specifically, DMN and SN behave antagonistically during the resting state condition (15, 24, 25). Conversely, high cross-network connectivity has been observed between SN and DMN nodes during resting state in a group of earthquake survivors (26). It has also been suggested that abnormal interconnectivity between DMN and SN could contribute to some PTSD symptoms, such as hyperarousal and avoidance (25).

More recent research on brain connectivity in psychiatric diseases has benefitted from the study of the relationships between neural biomarkers and clinical symptom scales. Several studies on PTSD moved towards this direction, relating post-trauma symptoms severity to neural correlates (13, 17, 27). In the present study, we aim at investigating the relationship between resting state large-scale network connectivity and post-trauma symptoms severity in traumatized individuals.

Since the relation between clinical scales scores and neural correlates may contribute to define the post-trauma individual profile, a special attention in this field should be paid to vulnerability and resilience measurements. Resilience refers to a dynamic process thanks to which individuals can positively adapt to a significantly adverse context, and can be able to grow despite adversities (6, 28, 29). This personal characteristic has been also defined as a multidimensional

phenomenon, encompassing internal locus of control, social problem-solving skills, sense of meaning, and self-esteem (30). The incidence of PTSD in the general population is low. When it is confronted with a traumatic episode, a minor part of subjects develops PTSD symptoms, whereas a spontaneous recovery occurs in a large part of the population (6). Among the individual differences, resilience represents the personal characteristic that could contribute to a positive post-trauma outcome. The comprehension of the neural mechanisms at the basis of resilience may provide valuable tools for prevention and treatment of post-trauma diseases. In his model of allostasis, Charney (2004) isolated eleven neurochemical, neuropeptide and hormonal possible mediators of the psychobiological response to stressors. Furthermore, the author examines the neural mechanism mediating reward, fear conditioning and social behavior circuits that are considered to be relevant to the character traits linked to resilience (28). Interestingly, as the author highlighted, the mPFC is the only brain structure involved in all three circuits. Nevertheless, a restricted number of studies searched a relationship between resilience and brain functioning. In an fMRI study on healthy subjects, Waugh and colleagues (2008) showed that participants with high-trait resilience exhibited a lower Insular activity with respect to the low-trait-resilience group in response to neutral stimuli following a threat cue, thus suggesting a rapid and appropriate evaluation of the neutral information (31). Another fMRI and perspective study investigated the predictive value of resilience for PTSD development, and the neural correlates underpinning the relation between resilience and post-trauma recovery in an acutely traumatized population (30). The authors found that resilience predicted PTSD symptoms at 5 - 6 weeks and at 3 months. Furthermore, they measured the relation between resilience score and BOLD response during trauma recall, revealing a significant relationship between trait resilience and right thalamus and inferior frontal gyrus, both involved in emotion regulation.

Finally, in his review, van der Werff proposed a model of functional and structural circuits putatively involved in resilience, highlighting that, among the studies on traumatized individuals, an

overlapping could be observed between the neural circuit of resilience and the one involved in emotion regulation (6). The author supposed that, from a functional point of view, an increased emotion upregulation (induced from mPFC) could be at the basis of individual resilience. Furthermore, this review indicates that the connectivity between amygdala-prefrontal cortex and other networks such as DMN or SN could play a primary role in resilience.

Considering on one hand the medial Prefrontal cortex key role in emotion regulation and resilience, and, on the other hand, the potential insight coming from the study of large scale network connectivity, an interesting contribution to the understanding of post-trauma recovery could be represented by the investigation of the relationship between resilience and resting state functional connectivity (RSFC) of mPFC, as a DMN node, with other networks. Nevertheless, to the best of our knowledge, no studies that directly correlate resting state functional connectivity to resilience have been so far conducted in a traumatized sample. Furthermore, the great majority of RSFC studies in PTSD have been carried on with fMRI, while only a few resting state magnetoencephalography (MEG) studies have been so far performed on PTSD.

MEG is a non-invasive high-resolution imaging technique whose advantages in clinical applications have been documented (32). In the past decade, the improvement of instruments and modeling technique developed in this field allowed a promising growth of MEG application to the characterization of neural mechanisms at the basis of several mental diseases. To date, findings from MEG resting state studies suggest atypical long-range hyperconnectivity in the high gamma band of resting state networks in PTSD patients compared to traumatized controls (33). Interestingly, another study by the same group revealed that PTSD severity positively correlated with gamma synchrony within the SN (34). These data encourage the use of MEG to look for MEG-based PTSD biomarkers, mainly connecting MEG results with clinical symptoms (32). Moreover, pharmaco-MEG, based on the changes in neuronal processing, induced by drug chemical

neuromodulation and measurable on the millisecond time-scale, has been successfully used in patients to understand brain pathologies and drug-treatment effects (35).

The present MEG study aims at directly investigating the relationship of resting state functional connectivity between the anterior frontal node of DMN (mPFC) and the whole brain with resilience, as measured by means of the Connor-Davidson resilience scale (CD-RISC) (36), and PTSD severity according with Clinician Administered PTSD Scale (CAPS) (37) in PTSD patients and Trauma Exposed Non-PTSD (TENP) participants. The functional connectivity approach we used, being based on the maximization of imaginary coherence (38), allows disclosing communication between segregated brain areas though synchrony in specific frequency channels. Moreover, this approach largely overcomes the well-known limitations to the study of functional connectivity due to signal mixing artifacts, i.e. any active brain source contributes to the signals measured at all sensors through volume spread (39-41). Based on the above evidence, a specific high-frequency cross-network behavior as a function of the resilience level and symptom severity is expected.

2. Methods and Materials

Participants and assessment

MEG data were recorded from 40 traumatized participants recruited from local health service. Twenty were drug-free outpatients with a DSM-IV-TR (1) diagnosis of PTSD and twenty were outpatients with trauma exposure who did not develop PTSD and thus represented the control group (TENP)..

Exclusion criteria were the following: current or lifetime diagnosis of organic mental disorder, schizophrenia, schizophreniform or other psychotic disorders, bipolar disorders, substance-related disorders, a current diagnosis of depressive disorder, uncontrolled or severe medical conditions, and any current or past psychopharmacological treatment.

The assessment included: the Clinician Administered PTSD Scale (CAPS) (37), the Connor-Davidson Resilience Scale (CD-RISC) (36), Hamilton Scale for Depression (HAM-D) (42), Hamilton Scale for Anxiety (HAM-A) (43) and Leeds Sleep Evaluation Questionnaire (L-SEQ) (44). All participants underwent the clinical examination carried out by an expert psychiatrist trained and certified in the use of the instruments. The Ethics Committee of the University "G. D'Annunzio" of Chieti-Pescara approved all recruitment and assessment procedures. All subjects included provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

Notably, in this study we focused on traumatized participants, who were otherwise healthy and without other psychiatric illnesses, and which were selected from a larger sample composed by 70 traumatized participants. This approach was designed to minimize the confounding of comorbidity or psychotropic medications on connectivity.

Procedures and Acquisition

MEG data were recorded by the whole-head 153-channel MEG system installed inside a magnetically shielded room at the Institute of Advanced Biomedical Technologies (ITAB), University "G. D'Annunzio" of Chieti-Pescara (45, 46). All signals were band-pass filtered at 0.16–250 Hz and digitized at 1 kHz.

The experimental paradigm consisted in 5 minutes of resting state, with the subjects sitting under the MEG scanner, keeping their eyes open and fixating a center black cross displayed on a white screen. The position of the subject's head was determined by acquiring the signal of five coils placed on the scalp. The positions of the coils and the anatomical landmarks were measured by a 3D digitizer (3Space Fastrak; Polhemus) for coregistration to magnetic resonance (MR) anatomical images. MR images were acquired after MEG, using a sagittal magnetization prepared rapid acquisition gradient echo T1-weighted sequence (MP-RAGE; Philips Achieva 3 T; TR 8.1 s, echo time TE 3.7 ms, flip angle 8°, voxel size 1x1x1 mm^3).

MEG data analysis

MEG data preprocessing was based on Independent Component Analysis as detailed in the Supplementary Material, and led to retaining nineteen out of twenty control subjects and nineteen out of twenty patients for functional connectivity analysis.

MEG functional connectivity analysis was based on a seed based approach, i.e. between the signal at the seed voxel and the signals at all other target brain voxels. The seed was chosen in the medial Prefrontal Cortex (mPFC), the frontal node of the Default Mode Network (47), located at coordinates - [2, 52, 23] - in MNI space. The functional connectivity values were derived from the Multivariate Interaction Measure – MIM (48, 49), a multivariate extension of the imaginary part of coherence (50). Details on the MIM metric and on the parameter settings used in this study are given in the Supplementary Material.

MIM measures the coupling between brain areas by revealing phase synchrony between their oscillatory activities in selected frequency bands (48, 51), a putative mechanism for neuronal communication both within neuronal assemblies and between different neuronal pools (52- 54).

In this work, functional connectivity through MIM was estimated for frequencies in the delta to gamma brain rhythms, i.e. from 2 to 100 Hz, and consecutive frequency bins were averaged over frequency bands, spanning the following ranges: delta (2-3 Hz), theta (4-7 Hz), low alpha (8-10 Hz), high alpha (10-12 Hz), beta (13-26 Hz), gamma (27-100 Hz). To assess voxel-wise statistical significance of connectivity, a non-parametric Wilcoxon signed-rank test was used ($p < 0.01$, Bonferroni corrected), leading to the identification of six whole-brain maps of connectivity to mPFC for the whole subject group. Details are given in the Supplementary Material. To assess possible differences in frequency specific connectivity patterns between the TENP and the PTSD groups, a two-tail t-test was performed for each band separately. Significant differences between groups were assessed by correction for multiple comparisons taking into account the average number across subjects of independent components ($p < 0.05$, Bonferroni corrected).

Finally, the values of functional connectivity to mPFC for all frequency bands were correlated with CD-RISC score and CAPS total score values, separately. This procedure was run considering all participants together, as well as for the two separated groups. For each brain voxel, a correlation value was obtained by calculating the Pearson correlation coefficient, and its significance, between the connectivity of that voxel to mPFC and the CD-RISC or CAPS scores. Correlation significance was further assessed by correction for multiple comparisons taking into account the average number of independent components ($p < 0.05$, Bonferroni corrected). This approach led to six whole-brain maps of correlation of the connectivity with mPFC with CD-RISC scores, and six with CAPS scores. To investigate specific cross-networks relation with resilience, a Pearson correlation analysis was also performed between the mean connectivity value between the DMN node (mPFC) and the SN nodes (dACC, bilateral Insular cortex) and resilience score in the

whole sample. Regions characterized by a significant connectivity with respect to mPFC were extracted from the above maps. To assess the strength of the correlations, a percentile-based bootstrap, with 10000 replicate samples, was performed to assess the 95% confidence intervals. To confirm the correlation results, a general regression model (GRM) analysis was also performed, entering the connectivity values as dependent variables, the psychometric scores (CD-RISC, CAPS, HAM-A, HAM-D, L-SEQ) as continuous predictors and the clinical condition (PTSD, TENP) as categorical modulator. A k-fold cross-validation approach (55) with k=10 was then applied to cross-validate the GRM results.

Demographic and Clinical Statistical Analysis

Differences in gender, trauma load, age, trauma distance and clinical features between the two groups were evaluated by using one-way Analysis of Variance (ANOVA). All statistical analyses were performed by Statistica 6.1 software (Statsoft Italia srl, 2003). Homogeneity of variance was assessed by means of the Brown-Forsythe test ($p<0.05$). Pearson correlation between all clinical scores was also performed and Bonferroni corrected. A percentile-based bootstrap, with 10000 replicate samples, was applied to assess the 95% confidence interval.

3. Results

Demographic and Clinical outcomes

The characteristics of the experimental groups are summarized in Table 1 and Supplementary Table 1. Patients and traumatized control groups did not differ in age, trauma load and trauma distance; groups also did not significantly differ in terms of gender: Chi square= 0.10 p=0.75. One-way ANOVA revealed that CAPS total score was statistically higher in PTSD patients than in traumatized controls [F (1-38)=66.12 p<0.0001]. Furthermore, PTSD and traumatized control groups differ in depression, anxiety and sleep quality scores. Specifically, both Hamilton A and Hamilton D scores (Anxiety and Depression respectively) were statistically higher for PTSD patients compared to traumatized controls: Hamilton A [F(1-38)=43.6 p<0.005]; Hamilton D [F(1-38)=38.44 p<0.001]. Finally, the L-SEQ total score was higher in traumatized controls than in PTSD patients [F(1-38)=4.3 p<0.05]. No statistical differences were observed between the two groups in the CD-RISC total score.

Table 1 Demographic and clinical characteristics of the two subject groups

	PTSD (N 20)		**TENP (N 20)**	
Number of females (%)	11 (55)		10 (50)	
	mean	*SD*	*mean*	*SD*
Age (ys)	36.1	10.19	37.35	9.8
Years from trauma (ys)	9.52	11.77	5.61	6.06
Trauma load	1.25	0.55	1.15	0.36
CAPS-tot	57.05*	15.08	16.45*	16.45
HAM-A	12.25*	7.44	5.6*	5.6
HAM-D	12.85*	6.70	5.7*	5.6
L-SEQ	-20.63*	64.53	24.45*	72.62
CD-RISC-tot	66.7	8.92	72.25	13.93

Note: Indices represent the results of ANOVA (p<0.05)

Whole group functional connectivity

Group functional connectivity maps for PTSD and TENP were similar for all frequency bands, and no significant differences between groups were observed. When the two groups are pooled together, a significant ($p < 0.05$, Bonferroni corrected) mPFC connectivity was observed with several regions in the low and high alpha and in the beta frequency bands. Specifically, for the low alpha frequency band, motor and pre-motor areas, intraparietal sulcus, insular cortex and posterior cingulate cortex in the left hemisphere and a medial frontal region (rostral Cigulate cortex/Supplementary Motor area) in the right hemisphere were significantly connected to mPFC. For the high alpha frequency band, a large portion of the bilateral parietal and occipital cortices was significantly connected to mPFC. For the beta frequency bands, bilateral medial frontal region (rostral Cigulate cortex/Supplementary Motor area), bilateral dorsolateral Prefrontal cortex, bilateral Intraparietal sulcus and bilateral inferior Temporal gyrus showed significant connectivity with mPFC.

Correlation connectivity – CAPS

Whole group correlation maps between mPFC connectivity and CAPS total score did not reach statistical significance. The same correlation performed separately for the two groups revealed that, in the beta band and in the traumatized control group, CAPS score positively correlated with connectivity of mPFC with left middle superior Frontal gyrus (lmSupFg), right Superior Temporal gyrus (rSTg) and some midline regions as Posterior Cingulate cortex/Precuneus (PCun), anterior medial Prefrontal cortex (ant-med PFC) and Anterior Cingulate cortex-medial Prefrontal cortex (ACC-mPFC): the higher the midline regions connectivity, the higher the post-traumatic symptom severity (Figure 1 and Supplementary Table 2). The percentile-based bootstrap approach on the correlations between CAPS and connectivity of mPFC to Pcun, ACC-mPFC, ant-

medPFC, rSTG resulted in an average confidence interval width of 0.823 (see Supplementary Table 2).

The General Linear Model (GRM) in which all the clinical scores were inserted as independent variables and the clinical condition (PTSD vs. TENP) as categorial variable evidenced that symptom severity together with resilience score significantly affect the observed functional connectivity between the midline regions (Table 2). Furthermore, GRM results also evidenced that group membership (PTSD vs TENP) significantly contributes to the observed functional connectivities. Conversely, HAM-A, HAM-D, L-SEQ scores did not significantly contribute to the observed connectivity, although these scores significantly differ between the PTSD and TENP groups. The result cross-validation showed that the average accuracy of the model is around 82% (see Table 2).

Finally, no significant correlation results were revealed by the PTSD group analysis alone.

Table 2: General Regression Model Analysis and k-fold Cross Validation in the regions resulting from correlation between mPFC connectivity and CAPS total score

			PCun1	lmSupFg	ACC-mPFC	ant-medPFC	rSTg
Whole model significance		Multiple R^2	0.438	0.395	0.391	0.429	0.429
		df (model, residual)	6, 31	6, 31	6, 31	6, 31	6, 31
		F	4.019	3.377	3.312	3.878	3.878
		p	**0.004**	**0.011**	**0.012**	**0.005**	**0.005**
Perameter estimates	CAPS	*Beta (ß)*	0.599	0.607	0.552	0.589	0.413
		t	2.183	2.133	1.933	2.130	1.495
		p	**0.037**	**0.041**	0.062	**0.041**	0.145
	CD-RISC	*Beta (ß)*	-0.422	-0.395	-0.377	-0.396	-0.462
		t	-2.715	-2.450	-2.334	-2.530	-2.950
		p	**0.011**	**0.020**	**0.026**	**0.017**	**0.006**
	HAM-A	*Beta (ß)*	0.213	0.193	0.152	0.334	0.166
		t	0.551	0.481	0.377	0.858	0.427
		p	0.586	0.634	0.709	0.398	0.673
	HAM-D	*Beta (ß)*	-0.319	-0.374	-0.256	-0.460	-0.062
		t	-0.894	-1.011	-0.689	-1.281	-0.173
		p	0.378	0.320	0.496	0.210	0.864
	L-SEQ	*Beta (ß)*	-0.152	-0.048	-0.100	-0.056	-0.028
		t	-0.820	-0.250	-0.517	-0.297	-0.152
		p	0.419	0.804	0.609	0.768	0.880
	Clinical cond	*Beta (ß)*	0.691	0.760	0.765	0.776	0.667
		t	2.950	3.127	3.137	3.288	2.826
		p	**0.006**	**0.004**	**0.004**	**0.003**	**0.008**
k-fold Cross-Validation accuracy % (k=10 ; mean= 81.6; sd= ±0.6)			**82**	**81.5**	**81.5**	**82**	**80.5**

[lmSupFg: left medial Superior Frontal gyrus; PCun1: Posterior Cingulate cortex/Precuneus; ACC-mPFC: Anterior Cingulate cortex-medial Prefrontal cortex; ant-medPFC: anterior medial Prefrontal cortex; rSTg: right Superior Temporal gyrus]

Correlation connectivity– CD-RISC

Whole group correlation maps between mPFC connectivity and CD-RISC score in beta are displayed in figure 2a. In this frequency band, a widespread negative correlation was observed between several lateral and medial regions connectivity to mPFC and CD-RISC score: the higher the connectivity of these regions to mPFC, the lower the resilience. In particular, a coupling negatively correlated with resilience was observed between mPFC and sensory-motor regions (bilateral V7, left Precentral gyrus-lPrec, left Middle Temporal gyrus-lMTg), posterior DMN node (PCun) and Salience Network nodes (bilateral Insular cortex-IC, dorsal Anterior Cingulate Cortex-dACC). To better represent the DMN-SN cross-networks relation with resilience, the subject level correlation analysis was displayed as scatterplot in figure 2b (Pearson coefficient r =-0.405, $p<0.05$). The percentile-based bootstrap approach on the correlations between CD-RISC and connectivity of mPFC to dACC, lINS, rINS, lMTg, lmPFC, lITg, rAntMTg, Pcun, lV7, rV7, lOCC, lSTG resulted in an average confidence interval width of 0.576± 0.042 (see Supplementary Table 3).

The correlation performed separately for the two groups revealed that the whole group results were mainly explained by the traumatized control group data. In this group, indeed, a correlation between brain connectivity to mPFC and CD-RISC score having a similar topography to that observed in the whole group was displayed, with the exception of the Salience Network areas (figure 3). No results were revealed by the PTSD group analysis alone.

The GRM in which all the clinical scores were inserted as independent variables and the clinical condition (PTSD vs. TENP) as categorial variable evidenced that resilience score significantly affects the observed functional connectivity between mPFC and all the regions displayed in Figure 2. The same model showed that also PTSD symptoms severity significantly affects the functional connectivity between mPFC and rAMTg, dACC and rV7 (see Table 3). As for the CAPS, group membership significantly contributes to the observed functional connectivities

while scores for anxiety, depression and sleep problems did not significantly contribute to the observed connectivity. The result cross-validation showed that the average accuracy of the model is around 81% (Table 3).

Table 3: General Regression Model Analysis and k-fold Cross Validation in those regions resulting from correlation between mPFC connectivity and CD-RISC total score

			dACC	**lINS**	**rINS**	**lPREC**	**lMTg**	**lmPFC**	**lITg**	**rAMTg**	**PCun2**	**lV7**	**rV7**	**lOCC**	**lSTg**
Whole model significance		Multiple R^2	0.439	0.357	0.453	0.395	0.421	0.420	0.423	0.442	0.407	0.370	0.403	0.384	0.356
		df (model, residual)	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31	6, 31
		F	4.041	2.869	4.284	3.378	3.760	3.744	3.782	4.089	3.545	3.038	3.481	3.221	2.862
		p	0.004	0.024	0.003	0.011	0.006	0.006	0.006	0.004	0.009	0.019	0.010	0.014	0.025
Perameter estimates	CAPS	*Beta (ß)*	0.623	0.448	0.522	0.407	0.525	0.480	0.499	0.579	0.506	0.516	0.578	0.484	0.389
		t	2.273	1.529	1.932	1.431	1.888	1.723	1.797	2.119	1.796	1.779	2.046	1.687	1.327
		p	**0.030**	0.136	0.063	0.162	0.068	0.095	0.082	**0.042**	0.082	0.085	**0.049**	0.102	0.194
	CD-RISC	*Beta (ß)*	-0.464	-0.430	-0.496	-0.424	-0.432	-0.458	-0.444	-0.462	-0.439	-0.432	-0.463	-0.469	-0.406
		t	-2.987	-2.587	-3.240	-2.634	-2.739	-2.905	-2.819	-2.984	-2.753	-2.631	-2.888	-2.884	-2.442
		p	**0.005**	**0.015**	**0.003**	**0.013**	**0.010**	**0.007**	**0.008**	**0.006**	**0.010**	**0.013**	**0.007**	**0.007**	**0.021**
	HAM-A	*Beta (ß)*	0.075	0.138	0.328	0.480	0.075	0.169	0.314	0.201	0.218	0.078	-0.028	0.149	-0.272
		t	0.195	0.334	0.861	1.199	0.192	0.432	0.803	0.523	0.550	0.190	-0.070	0.368	-0.659
		p	0.847	0.741	0.396	0.240	0.849	0.669	0.428	0.605	0.586	0.850	0.945	0.716	0.515
	HAM-D	*Beta (ß)*	-0.279	-0.205	-0.570	-0.559	-0.153	-0.323	-0.476	-0.279	-0.307	-0.257	-0.191	-0.336	0.214
		t	-0.785	-0.539	-1.622	-1.511	-0.423	-0.892	-1.317	-0.785	-0.837	-0.680	-0.519	-0.901	0.560
		p	0.439	0.594	0.115	0.141	0.675	0.379	0.197	0.438	0.409	0.501	0.608	0.375	0.580
	L-SEQ	*Beta (ß)*	-0.058	-0.132	-0.093	-0.136	-0.185	-0.147	-0.149	-0.046	-0.135	-0.148	-0.164	-0.142	-0.226
		t	-0.315	-0.668	-0.508	-0.707	-0.983	-0.781	-0.791	-0.250	-0.707	-0.753	-0.856	-0.733	-1.137
		p	0.755	0.509	0.615	0.485	0.333	0.441	0.435	0.804	0.485	0.457	0.399	0.469	0.264
	Clinical cond	*Beta (ß)*	0.753	0.558	0.648	0.557	0.646	0.671	0.647	0.723	0.638	0.622	0.601	0.559	0.573
		t	3.220	2.228	2.808	2.293	2.717	2.822	2.726	3.099	2.653	2.511	2.487	2.281	2.285
		p	**0.003**	**0.033**	**0.009**	**0.029**	**0.011**	**0.008**	**0.010**	**0.004**	**0.012**	**0.017**	**0.018**	**0.030**	**0.029**
k-fold Cross-Validation accuracy % (k=10 ; mean= 81; sd= ± 1.4)			**81.5**	**80**	**82.5**	**81.5**	**81.5**	**82**	**82**	**81.5**	**82**	**80.5**	**80.5**	**81**	**77**

[dACC: dorsal Anterior Cingulate Cortex; r and l IC: right and left Insular cortex; lPrec: left Precentral gyrus; lMTg: left Middle Temporal gyrus; lmPFC: left medial Prefrontal cortex; lITg: left Inferior Temporal gyrus; rAntMTg: right anterior Middle Temporal gyrus; PCun2: Posterior Cingulate cortex/Precuneus; r and l V7: visual area 7; lOCC: left Occipital area; lSTg: left Superior Temporal gyrus]

4. Discussion

The goal of our study was to investigate the specific relation of resilience and PTSD symptom severity with resting state functional connectivity in traumatized participants with and without PTSD development using the high temporal resolution deriving from MEG technique, which offers the possibility to explore high frequency oscillations.

In this framework, relationships between connectivity and symptoms severity can help to better understand the prognostic potential of the method and the brain dynamics underlying the pathology. In our study, frontal DMN connectivity has been correlated with PTSD severity measured by means of CAPS scale. In this study, the TENP group could represent the resilient group, following the term meaning used by van der Werff (6). Indeed, even if in this case the measured resilience score failed to differ between the two groups, trauma exposed individuals which have not developed PTSD can be considered to have the capacity to positively react to a traumatic event and avoid its negative consequences (6). Our results clearly indicate that, in the TENP group, as symptoms severity increases, the connectivity between midline regions increases as well in the beta band. This evidence is concordant with previous findings deriving from fMRI studies. Specifically, Lanius and colleagues suggested that resting state functional connectivity of the posterior node of DMN with anterior medial regions and amygdala was associated with current PTSD symptoms (17). Interestingly, medial brain regions have been observed to be inter-connected during self-referential information processing (12, 56- 58). In a recent review (59) the involvement of midline regions in self-specific activity has been highlighted. The authors also demonstrated the strong overlap between these self-related regions and DMN nodes, specifically in the anterior aspect. The perigenual anterior cingulated cortex (PACC) has been considered as the hub of self-related processing, together with mPFC and PCC also implicated in familiar and self processing. In our TENP group, the correspondence between increased symptoms severity and increased connectivity between regions related to self-referential processing and self perception could suggest

that, as a consequence of traumatic experience, an exaggerated self-referenced status could represent a risk factor for symptoms manifestation, even without full PTSD development. Furthermore, these findings with mPFC were significant in the beta frequency band, thus possibly indicating the association of beta oscillatory activity with the predominance of endogenous top-down processing in this region. Engel & Fries (2010) (60) highlighted that beta band activity is related to the maintenance of a given cognitive status, and that the enhancement of that activity reflects endogenous vs exogenous components of subject status, as shown in our previous study on social cognition (61). Moreover, beta band connectivity in networks involving both early and higher order cortical areas serves maintenance of the cognitive status by synchronizing the activity of the recruited brain areas (60). Based on the results from the present study, we would thus suggest that the enhanced connectivity in the beta band observed in the midline regions in function of symptoms severity may reflect the abnormal persistence of the *status quo*.

Contrarily to the expectance, these results did not reach statistical significance within the PTSD group. This could likely explain the large confidence interval revealed by bootstrap percentile based analysis on the whole group (thus pooling togheter PTSD and TENP). The reasons of the lack of significance in PTSD could be various: first, symptoms expression could increase the sample heterogeneity and variability in PTSD group, thus reducing the statistical power measured within group; furthermore, the well-known involvement of subcortical activity (amygdala, hippocampus) in PTSD pathophysiology could have reduced the general cortico-cortical connectivity in this group, since the MEG has scarce sensitivity to deep source activity (62). Finally, an alternative explanation may be that the increased activity of mPFC has been suggested to be typical of after-trauma resilient subjects, suggesting that this region represents a neural marker in trauma-related resilience (9), thus explaining the lack of evidence for mPFC connectivity in the PTSD group.

Furthermore, our data indicate that, in the whole traumatized group (pooling together PTSD and TENP, thus regardless symptom development), a negative correlation exists between DMN connectivity and sensory-motor regions in the beta band. These data are coherent with the observation of heightened sensorial areas activation in traumatized groups as a consequence of trauma (9).

Considering the whole group correlation maps, another interesting information arises: the post trauma resilience score was inversely correlated with between-network connectivity. Specifically, the results suggest that, in our traumatized participants, the higher the resilience, the lower the cross-network connectivity between anterior DMN and three Salience Network (SN) core nodes (dorsal anterior cingulated cortex-dACC, right and left insular cortex). The Salience Network is a large-scale network encompassing the anterior insula and the dorsal ACC, over some subcortical regions, and it is considered a central system focused on the identification of biologically and cognitively relevant information for a coherent and flexible behavior and self-awareness (63). The physiological interplay between DMN and SN during various cognitively demanding tasks seems to show an antagonistic behavior (SN increasing with DMN decreasing) (14, 24). Critically, an adequate SN functioning in mediating the dynamic interplay across networks is necessary for an efficient DMN suppression during cognitive tasks, thus allowing a goal-directed behavior (63). In general, inappropriate assignment of salience to external or internal stimuli caused by SN dysfunction has been highlighted in different mental disorders, including schizophrenia and anxiety disorders (23). In PTSD, an aberrant interconnectivity between DMN and SN may be at the basis of altered self-referential mental activity (e.g. recurring thoughts, memories, etc). In an fMRI study, Sripada and colleagues (2012) (25) demonstrated an increased coupling between the DMN and SN in returning veterans with PTSD, suggesting an alteration within the interaction between large-scale brain networks (see also Peterson et al. 2014 for a review) (22).

Of note, our results indicate a negative correlation between DMN-SN connectivity and resilience. One could speculate that resilience represents a protective factor to the aberrant cross network communication. Indeed, the issue regarding whether people develop posttraumatic symptoms after experiencing a traumatic event – in other words: why some people are vulnerable to stressors and trauma and some other not – remains unclear right now. Recent findings coming from the epigenetic field have shed new light on this issue (64-66), but also a role for resilience in individual stressors coping skills has been clearly demonstrated. Resilience as a trait characteristic has been found to reduce risk for posttraumatic stress disorder among individuals who experienced childhood abuse (67). Furthermore, the effects of resilience on the likelihood of developing PTSD in an inner-city sample of primary care patients has been assessed, demonstrating that a resilience high score was associated with a decreased likelihood of PTSD (68). Finally, a recent fMRI study demonstrated that resilience predicted PTSD symptoms severity at 5 to 6 weeks and at 3 months post-trauma, suggesting that resilience is a significant predictor of PTSD symptoms severity and could mediate the influence of childhood trauma on posttraumatic adjustment (30).

These finding are also supported by our further results derived by the TENP single group correlation. Here the whole-group negative correlation between resilience and DMN-SN cross-interaction disappears, thus reinforcing the hypothesis of a protective role of resilience for brain functioning. Indeed, although the lack of statistically significant differences between groups in the resilience score, our TENP group represents, among the whole traumatized participants, the one with an average higher resilience that is likely to have allowed them to resist to full PTSD manifestation. Looking at our findings as a continuum between healthy and pathological after trauma outcomes, we suggest a relationship between resilience and a good dialog between those networks needed to face a traumatic event and its long-term consequence on the individual psychological life. Reinforcing subjective coping ability by means of an adequate psychotherapy could represent an efficacious approach to post-traumatic treatment.

This study presents some limitations. First, we are aware of the rather small sample size of our research that could limit the conclusion derived from our results. Nevertheless, as mentioned above, the participants' selection was focused on traumatized participants who were otherwise healthy and without other psychiatric illnesses and without any current or past psychopharmacological treatment. They were selected from a larger sample composed by 70 traumatized participants. This approach was designed to minimize the confounding of comorbidity or psychotropic medications on connectivity. Furthermore, the cross-sectional nature of this study could represent a further limitation. For example, the conceptualization of resilience is still at an early stage. Whether resilience could be considered a stable trait it is not yet confirmed. Consequently, our findings on the interplay between brain connectivity and resilience level after trauma should be re-considered along time. Indeed, even if our results are reinforced by the regression analysis, a longitudinal study assessing the relation between brain connectivity and resilience or PTSD severity could dispel any doubt on the intrinsic nature of this relation.

In conclusion, the present study moved from the question on why some people develop PTSD after trauma and some others do not. Far from a definitive answer, we can however meditate on the psychological, subjective meaning of a traumatic event for the individual. The salience attributed to a single event could be different from person to person, and the aberrant saliency detection surely has important repercussions on the consequent reaction to the context. The relationship here observed between self-referential and saliency systems seems to indicate that a self-referred reading of the environment represents a maladaptive strategy to react to trauma, and that such a reading could be part of a general low resilience level. These findings convey a new valuable insight: understanding how the resting state networks operate may help to provide more targeted drugs and behavioral treatments for post-traumatic disorders.

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References

1. American Psychiatric Association (2000): *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition-Text Revision, Washington DC.
2. Lanius RA, Bluhm R, Lanius U, Pain C (2006): A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *J Psychiatr Res* 40(8): 709-729.
3. Williams LM, Kemp AH, Felmingham K, Barton M, Olivieri G, Peduto A, *et al.* (2006): Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. *Neuroimage* 29(2):347–357.
4. Brunetti M, Sepede G, Mingoia G, Catani C, Ferretti A, Merla A , *et al.* (2010): Elevated response of human amygdala to neutral stimuli in mild post traumatic stress disorder: neural correlates of generalized emotional response. *Neuroscience* 168(3), 670-679.
5. Milad MR, Quirk GJ (2002): Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*; 420, 70–74.
6. van der Werff, SJ, van den Berg SM, Pannekoek JN, Elzinga BM, Van Der Wee NJ (2013): Neuroimaging resilience to stress: a review. *Frontiers Behav Neurosci* 7;7:39.
7. Brunetti M, Sepede G, Ferretti A, Mingoia G, Romani G L, Babiloni C (2015): Response inhibition failure to visual stimuli paired with a “single-type” stressor in PTSD patients: An fMRI pilot study. *Brain Res Bull* 114, 20-30.
8. Rauch SL, Shin LM, Phelps EA (2006): Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research-past, present, and future. *Biol Psychiatry* 15;60(4):376-82.
9. Patel R, Spreng RN, Shin LM, Girard TA (2012): Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev* 36(9):2130-42.
10. Lanius RA, Williamson PC, Densmore M, Boksman K, Neufeld RW, Gati JS, *et al.* (2004) RS: The nature of traumatic memories: a 4-T FMRI functional connectivity analysis. *Am J Psychiatry* 161(1):36-44.

11. Xiong K, Zhang Y, Qiu M, Zhang J, Sang L, Wang L, *et al.* (2013): Negative emotion regulation in patients with posttraumatic stress disorder. *PLoS One* 13;8(12):e81957.

12. Ramage AE, Laird AR, Eickhoff SB, Acheson A, Peterson AL, Williamson DE, *et al.* (2013): A coordinate-based meta-analytic model of trauma processing in posttraumatic stress disorder. *Hum Brain Mapp* 34(12):3392-9.

13. Reuveni I, Bonne O, Giesser R, Shragai T, Lazarovits G, Isserles M, *et al.* (2016): Anatomical and functional connectivity in the default mode network of post-traumatic stress disorder patients after civilian and military-related trauma. *Hum Brain Mapp* 37(2):589-99.

14. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proc Natl Acad Sci USA* 98:676–682.

15. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA* 102: 9673–9678.

16. Calhoun VD, Kiehl KA, Pearlson GD (2008): Modulation of temporally coherent brain networks estimated using ICA at rest and during cognitive tasks. *Hum Brain Mapp* 29:828–838.

17. Lanius RA, Bluhm RL, Coupland NJ, Hegadoren KM, Rowe B, Théberge J, *et al*. (2010): Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatr Scand* 121(1):33-40.

18. Bluhm RL, Miller J, Lanius R A, Osuch E A, Boksman K, Neufeld RWJ, *et al.* (2007): Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. *Schizophr Bull* 33, 1004–1012.

19. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, Reiss AL, et al. (2007): Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulated cortex and thalamus. *Biol Psychiatry* 62: 429–437.

20. Zhao XH, Wang PJ, Li CB, Hu Z-H, Xi Q, Wu W-Y *et al*. (2007): Altered default mode network activity in patients with anxiety disorders: an fMRI study. *Eur J Radiol* 63, 373–378.

21. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga - Barke E J (2009): Default-mode brain dysfunction in mental disorders: A systematic review. *Neurosci Biobehav Rev* 33:279–296.

22. Peterson A, Thome J, Frewen P, Lanius RA (2014): Resting-state neuroimaging studies: a new way of identifying differences and similarities among the anxiety disorders? *Can J Psychiatry* 59(6):294-300.

23. Menon V (2011): Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci* 15(10):483-506.

24. Greicius MD, Krasnow B, Reiss AL, Menon V (2003): Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100:253–8.

25. Sripada RK, King AP, Welsh RC, Garfinkel SN, Wang X, Sripada CS, *et al*. (2012): Neural Dysregulation in Posttraumatic Stress Disorder: Evidence for Disrupted Equilibrium between Salience and Default Mode Brain Networks. *Psychosom Med* 74(9):904-911.

26. Yin Y, Jin C, Hu X, Duan L, Li Z, Song M, *et al.* (2011): Altered resting-state functional connectivity of thalamus in earthquake-induced posttraumatic stress disorder: a functional magnetic resonance imaging study. *Brain Res* 1411:98-107.

27. Dunkley BT, Doesburg SM, Jetly R, Sedge PA, Pang EW, Taylor MJ et al. (2015): Characterizing intra- and inter-intrinsic network synchrony in combat-related post-traumatic stress disorder. *Psychiatry Res* 234:172–81.

28. Charney DS (2004): Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am.J.Psychiatry* 161, 195–216.

29. Curtis WJ, Cicchetti D (2003): Moving research on resilience into the 21st century: theoretical and methodological considerations in examining the biological contributors to resilience. *Dev Psychopathol* 15, 773–810.

30. Daniels JK, Hegadoren KM, Coupland NJ, Rowe BH, Densmore M, Neufeld RW, et al. (2012): Neural correlates and predictive power of trait resilience in an acutely traumatized sample: a pilot investigation. *J Clin Psychiatry* 73(3):327-32.

31. Waugh CE, Wager TD, Fredrickson BL, Noll DC, Taylor SF (2008): The neural correlates of trait resilience when anticipating and recovering from threat. *Soc Cogn Affect Neurosci* 3(4):322-32..

32. Wilson TW, Heinrichs-Graham E, Proskovec AL, McDermott TJ (2016): Neuroimaging with magnetoencephalography: A dynamic view of brain pathophysiology. *Transl Res* 175:17-36.

33. Dunkley BT, Doesburg SM, Sedge PA, Grodecki RJ, Shek PN, Pang EW, *et al.* (2014): Resting-state hippocampal connectivity correlates with symptom severity in posttraumatic stress disorder. *Neuroimage Clin* 5:377-84.

34. Dunkley BT, Doesburg SM, Jetly R, Sedge PA, Pang EW, Taylor MJ et al. (2015): Characterizing intra- and inter-intrinsic network synchrony in combat-related post-traumatic stress disorder. *Psychiatry Res* 234:172–81.

35. Muthukumaraswamy SD (2014): The use of magnetoencephalography in the study of psychopharmacology (pharmaco-MEG). *J Psychopharmacol* 28(9):815-29.

36. Connor KM, Davidson JR (2003): Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety* 18(2):76-82.

37. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, *et al.* (1995): The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress* 8(1), 75-90.

38. Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallet M (2004): Identifying true brain interaction from EEG data using the imaginary part of coherency. *Clin Neurophysiol* 115:2292-2307.

39. Marzetti L, Nolte G, Perrucci MG, Romani GL, Del Gratta C (2007): The use of standardized infinity reference in EEG coherency studies. *Neuroimage* 15; 36(1):48-63.

40. Schoffelen, JM, Gross J (2009): Source connectivity analysis with MEG and EEG. *Hum Brain Mapp* 30(6):1857-65.

41. Sekihara K, Owen JP, Trisno S, Nagarajan SS (2011): Removal of spurious coherence in MEG source-space coherence analysis. *IEEE Trans Biomed Eng* 58(11):3121-9.

42. Hamilton M (1967): Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278.

43. Hamilton M (1959): The assessment of anxiety states by rating. *Brit J Med Psychol* 32:50.

44. Parrott AC, Hindmarch I (1978): Factor analysis of a sleep evaluation questionnaire. *Psychol Med* 8: 325–329.

45. Pizzella V, Della Penna S, Del Gratta C, Romani, GL (2001): SQUID systems for biomagnetic imaging. *Supercond Sci Tech* 14(7): R79-R114.

46. Chella F, Zappasodi F, Marzetti L, Della Penna S, Pizzella V (2012): Calibration of a multichannel MEG system based on the signal space separation method. *Phys Med Biol* 7;57(15):4855-70.

47. Buckner RL, Andrews-Hanna JR, Schacter DL (2008): The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124:1-38.

48. Marzetti, L, Della Penna S, Snyder AZ, Pizzella V, Nolte G, de Pasquale F, *et al*. (2013): Frequency specific interactions of MEG resting state activity within and across brain networks as revealed by the Multivariate Interaction Measure. *Neuroimage* 79:172-83.

49. Ewald A, Marzetti L, Zappasodi F, Meinecke FC, Nolte G (2012): Estimating true brain connectivity from EEG/MEG data invariant to linear and static transformations in sensor space. *Neuroimage* 60: 476–488.

50. Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallet M (2004): Identifying true brain interaction from EEG data using the imaginary part of coherency. *Clin Neurophysiol* 115:2292-2307.

51. Marzetti L, Di Lanzo C, Zappasodi F, Chella F, Raffone A, Pizzella V (2014): Magnetoencephalographic alpha band connectivity reveals differential default mode network interactions during focused attention and open monitoring meditation. *Front Hum Neurosci* 15; 8:832.

52. Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001): The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2(4):229-39.

53. Engel AK, Gerloff C, Hilgetag CC, Nolte G (2013): Intrinsic coupling modes: multiscale interactions in ongoing brain activity. *Neuron* 20;80(4):867-86.

54. Fries P (2015): Rhythms for cognition: communication through coherence. *Neuron* 88 (1), 220-235.

55. Jung Y, Hu JH (2015) A K-fold averaging cross-validation procedure. *Journal of Nonparametric Statistics* 27:167–79.

56. Sajonz B, Kahnt T, Margulies DS, Park SQ, Wittmann A, Stoy M, *et al.* (2010): Delineating self-referential processing from episodic memory retrieval: common and dissociable networks. *Neuroimage* 50(4):1606–1617.

57. Tursich M, Ros T, Frewen PA, Kluetsch RC, Calhoun VD, Lanius RA (2015): Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. *Acta Psychiatr Scand* 132(1):29-38.

58. Meshi D, Mamerow L, Kirilina E, Morawetz C, Margulies DS, Heekeren HR (2016): Sharing self-related information is associated with intrinsic functional connectivity of cortical midline brain regions. *Sci Rep* 7;6:22491.

59. Qin P, Northoff G (2011): How is our self related to midline regions and the default-mode network? *Neuroimage* 1;57(3):1221-33.

60. Engel AK, Fries P (2010): Beta-band oscillations-signalling the status quo? Current Opinion in *Neurobiology* 20(2):156-65.

61. Brunetti M, Zappasodi F, Marzetti L, Perrucci MG, Cirillo S, Romani GL, *et al.* (2014): Do you know what I mean? Brain oscillations and the understanding of communicative intentions. *Front Hum Neurosci* 4;8:36.

62. Del Gratta C, Pizzella V, Torquati K, Romani GL (1999): New trends in magnetoencephalography. *Electroencephalogr Clin Neurophysiol Suppl* 50:59-73.

63. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct* 214(5-6):655-67.

64. Angelucci F, Ricci V, Gelfo F, Martinotti G, Brunetti M, Sepede G, *et al.* (2014): BDNF serum levels in subjects developing or not post-traumatic stress disorder after trauma exposure. *Brain Cogn* 84(1):118-22.

65. Martinotti G, Sepede G, Brunetti M, Ricci V, Gambi F, Chillemi E, et al. (2015): BDNF concentration and impulsiveness level in post-traumatic stress disorder. *Psychiatry Res* 229(3):814-8.

66. Stratta P, Sanità P, Bonanni RL, de Cataldo S, Angelucci A, Rossi R, *et al.* (2016): Clinical correlates of plasma brain-derived neurotrophic factor in post-traumatic stress disorder spectrum after a natural disaster. *Psychiatry Res* 12;244:165-170.

67. Wingo AP, Ressler KJ, Bradley B (2014): Resilience characteristics mitigate tendency for harmful alcohol and illicit drug use in adults with a history of childhood abuse: a cross-sectional study of 2024 inner-city men and women. *J Psychiatr Res* 51:93-9.

68. Wrenn GL, Wingo AP, Moore R, Pelletier T, Gutman AR, Bradley B, *et al.* (2011): The effect of resilience on posttraumatic stress disorder in trauma-exposed inner-city primary care patients. *J Natl Med Assoc* 103(7):560-6.

Captions

Figure 1: Correlation maps between mPFC – medial Prefrontal cortex - connectivity (the black dot indicates the position of the seed used to calculate brain connectivity) and CAPS total score in the beta band and in the trauma exposed non PTSD group (TENP). CAPS score was positively correlated with connectivity of mPFC with midline regions. [lmSupFg: left medial Superior Frontal gyrus; PCun: Posterior Cingulate cortex/Precuneus; ACC-mPFC: Anterior Cingulate cortex-medial Prefrontal cortex; ant-medPFC: anterior medial Prefrontal cortex; rSTg: right Superior Temporal gyrus].

Figure 2: a) Whole group (TENP and PTSD pooled together) correlation maps between mPFC – medial Prefrontal cortex - connectivity (the black dot indicates the position of the seed used to calculate brain connectivity) and CD-RISC total score in the beta frequency band. A negative correlation of CD-RISC score and connectivity of mPFC was observable in the follow regions: left Precentral gyrus (lPrec); left Superior Temporal gyrus (lSTg); left medial Prefrontal cortex (lmPFC); left Middle Temporal gyrus (lMTg); left and right Insular cortex (lIC and rIC repectively); left Inferior Occipital gyrus (lIOcc); dorsal Anterior Cingulate cortex (dACC); bilateral Posterior Cingulate cortex/Precuneus (PCun); right and left Visual area 7(rV7 and lV7 respectively); left Inferior Temporal gyrus (lITg); right Anterior Middle Temporal gyrus (rAntMTg). **b)** Scatterplot of Pearson correlation between the mean connectivity in DMN and SN nodes and CD-RISC total score in the whole sample (TENP and PTSD pooled together) [Pearson correlation; N=39, r=-0.405; $p<0.05$].

Figure 3: TENP group correlation maps between mPFC – medial Prefrontal cortex - connectivity (the black dot indicates the position of the seed used to calculate brain connectivity) and CD-RISC total score in the beta frequency band. A negative correlation of CD-RISC score and connectivity of mPFC was observable in the follow regions: left Precentral gyrus (lPrec); left medial Prefrontal cortex (lmPFC); left Middle Temporal gyrus (lMTg); bilateral Posterior Cingulate cortex/Precuneus (PCun); left Inferior Temporal gyrus (lITg); right Anterior Middle Temporal gyrus (rAntMTg).

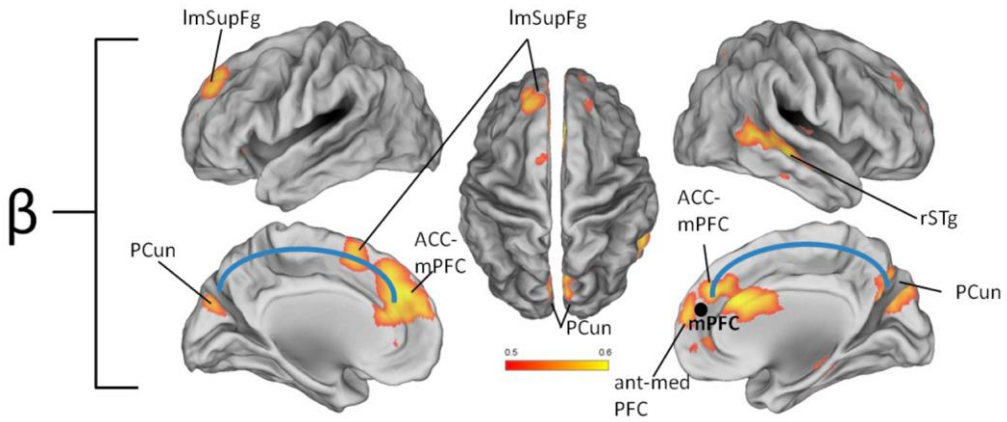
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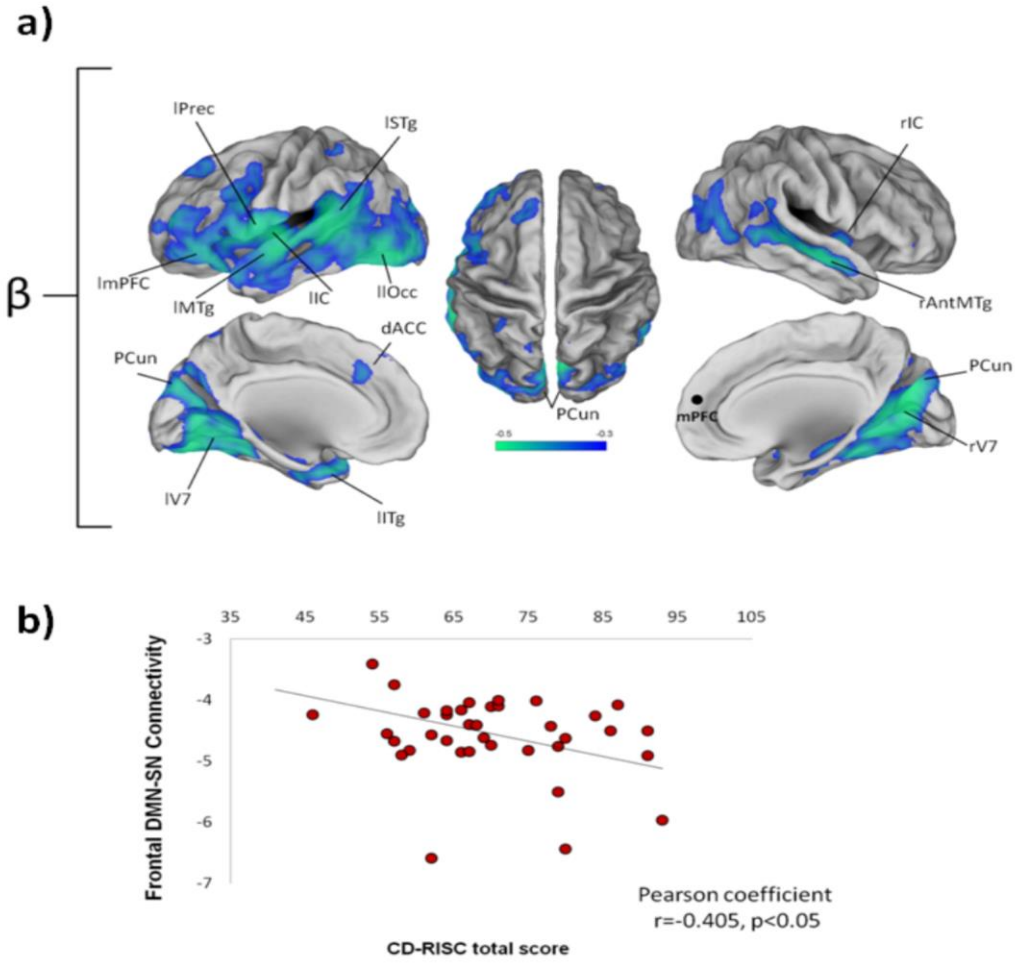
Figure 1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PCun
mPFC
rV7
b)
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-7
Frontal DMN-SN Connectivity
Pearson coefficient
r=-0.405, p<0.05
CD-RISC total score

Figure 2

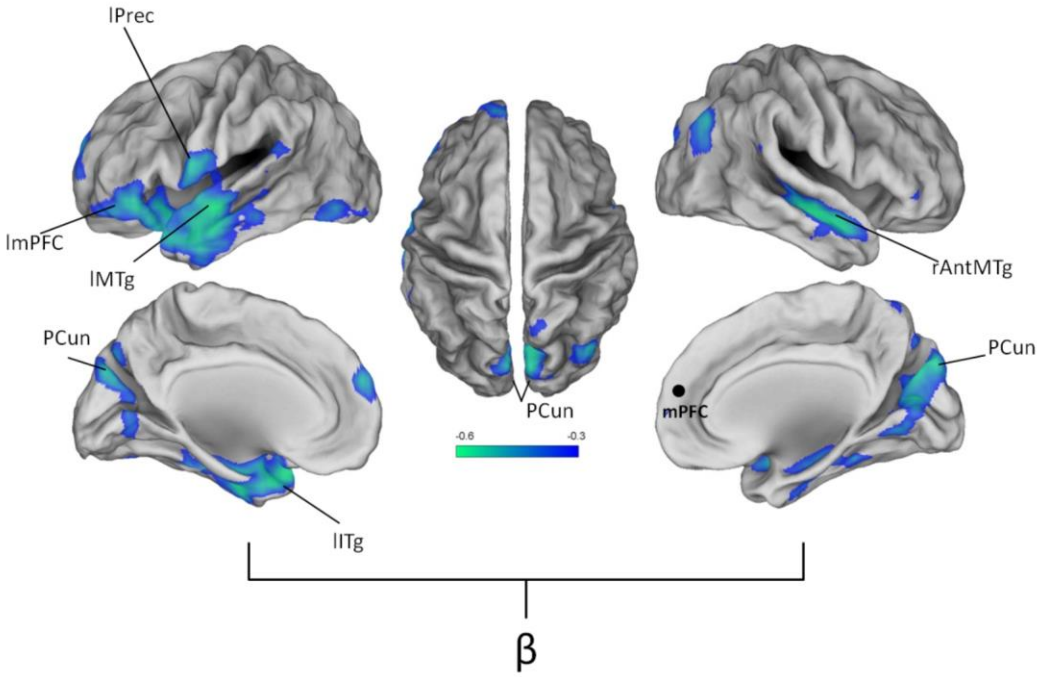

Figure 3